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A prospective open-labeled trial with levetiracetam in pediatric epilepsy syndromes: Continuous spikes and waves during sleep is definitely a target

S. Chhun [a,b,c], P. Troude [d], N. Villeneuve [e], C. Soufflet [a,b,f], S. Napuri [g], J. Motte [h], F. Pouplard [i], C. Alberti [d], S. Helfen [j], G. Pons [a,b,c], O. Dulac [a,b,k], C. Chiron [a,b,k,*]

[a] Inserm, U663, Paris, France
[b] University Paris Descartes, Faculty of Medicine, Paris, France
[c] APHP, Pediatric Clinical Pharmacology, Cochin-Saint Vincent de Paul Hospital, Paris, France
[d] APHP, Unit of Clinical Research, Robert Debre Hospital, Paris, France
[e] APHM, Neuropediatric Department, Marseille, France
[f] APHP, Necker Hospital, Department of Functional Explorations, Paris, France
[g] Neuropediatric Department, Rennes Hospital, France
[h] Neuropediatric Department, American Memorial Hospital, Reims, France
[i] Neuropediatric Department, Angers Hospital, France
[j] APHP, Necker Hospital, Unit of Clinical Research, Paris, France
[k] APHP, Necker Hospital, Neuropediatric Department, Paris, France

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ABSTRACT

Although LVT is currently extensively prescribed in childhood epilepsy, its effect on the panel of refractory epilepsy syndromes has not been entirely evaluated prospectively. In order to study the efficacy and safety of LVT as adjunctive therapy according to syndromes, we included 102 patients with refractory seizures (6 months to 15 years) in a prospective open-labeled trial. The responder rate was respectively 36% and 32% at 3 and 6 months with 6% and 7% patients becoming seizure free. Among the responders at 6 months ($n = 33$), seizure frequency decreased by 66% and 79% at 3 and 6 months LVT compared to baseline. The highest benefit was for CSWS patients with 2/3 responders, 50% seizure free and no aggravation. LVT provided respectively 39% and 42% responders in focal and absence epilepsies. Infantile spasms and Dravet syndrome experienced the lowest efficacy. No patient with myoclonic-astatic epilepsy or Lennox–Gastaut syndrome was aggravated. LVT dose over 40 mg/kg/d was associated with a lower response rate. Tolerability was excellent. In spite of a small sample, we assume that CSWS is a good candidate for a randomized-controlled trial with LVT.

1. Introduction

Among the new antiepileptic drugs evaluated in children over the past 20 years, levetiracetam (LVT) is quite remarkable for many reasons. After the US Food and Drug Administration and the European Medicines Agency approval as adjunctive therapy for epilepsy with refractory partial onset seizures (POS) in children aged 4–16 years,[1] it was also the first to be approved in infants aged 1 month to 4 years.[2] LVT has a large spectrum of action and its effect was also shown to expand to adolescent idiopathic generalized epilepsy (IGE), namely juvenile myoclonic epilepsy, juvenile absence epilepsy and generalized tonic–clonic seizures of awakening.[3–5] LVT can be co-administered with any drug since it is not metabolized by the hepatic cytochrome P450 system.[6] Because of its favorable safety profile and lack of impact on child cognition,[7] LVT monotherapy studies are emerging in idiopathic epilepsies: LVT proved to be as efficient as oxcarbazepine in BECTS (benign epilepsy with centro-temporal spikes)[8] and preliminary open prospective data suggested that it might be useful as first line in Jeavons syndrome (eyelid myoclonia with absences), Panayiotopoulos syndrome, and occipital epilepsy of Gastaut type.[9–13]

Besides these two major groups of pediatric epilepsy patients, refractory Epilepsy with POS and idiopathic generalized/partial epilepsy, epileptic encephalopathy represent a third group, highly refractory and specific to pediatrics.[14] However, in none of them is there any controlled trial performed with LVT. Although open-labeled prospective studies are still scarce, they suggest that LVT

* Corresponding author at: U663, Service de Neurologie et Metabolisme, Hopital Necker, 149 rue de Sevres, 75015 Paris, France. Tel.: +33 1 42192700; fax: +33 1 42192874.
E-mail address: catherine.chiron@nck.aphp.fr (C. Chiron).

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may benefit to 35–44%[9,15] of patients with epileptic encephalopathy and that Dravet syndrome may be a target.[16] Among the many retrospective data drawn from large series of children with pharmaco-resistant epilepsy,[17–21] several studies identified the epileptic encephalopathy with CSWS (continuous spikes and waves during sleep) as a potential candidate for LVT therapy.[22–27] However, this syndrome has not been prospectively studied so far.

To further evaluate the efficacy of LVT in the entire panel of pediatric epilepsy syndromes, we performed a prospective open-labeled study of LVT as adjunctive therapy in a large and non-selected population of children aged from 6 months to 15 years with refractory seizures.

2. Materials and methods

2.1. Study design

Patients were recruited from five French centers for pediatric third-line epilepsy care. The study was approved by the Paris-Cochin ethics committee and was carried out in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice. The study was designed and built directly by the clinicians, and it was sponsored by FFRE (French Foundation for Research in Epilepsy). The trial was not included in the plan of development of UCB Pharma which nevertheless partially funded it. Inclusion criteria were the following: (1) age between 6 months and 15 years, (2) from one to a maximum of three AEDs at a stable dosage for at least one month, (3) countable seizures, (4) pharmaco-resistant epilepsy with the persistence of at least 8 seizure a month, at a stable frequency for 1 month before the inclusion, and (5) written consent from parents or legal guardian, who had to be able to record seizures in a diary. The type of epilepsy was determined based on seizure types as partial or generalized and based on epilepsy syndrome classification (ILAE classification, 1989) as Epilepsy with POS, epilepsy with continuous spikes and waves during sleep (CSWS), absence epilepsy (including childhood absence epilepsy and epilepsy with myoclonic absences), Infantile spasms, Dravet syndrome, Lennox–Gastaut syndrome, myoclonic-astatic epilepsy, and other generalized epilepsies or unclassified.

The study comprised three phases: a 1 month baseline period was followed by a 1 month titration period and a 5 month evaluation period. Efficacy and safety were assessed at 3 and 6 months. Later on, the child could be maintained on LVT for long-term, at the discretion of the investigator. During the titration period, LVT was added to the baseline therapy at the starting dose of 10 mg/kg (20 mg/kg for infants under 2 years) daily for two weeks, and then titrated to 20 mg/kg (40 mg/kg for under 2 years) daily for two weeks to the final dose of 40 mg/kg (60 mg/kg for under 2 years). The LVT dose was not increased in case of complete seizure control and could be decreased in case of side effects. The final dose regimen that was reached was maintained unchanged during the first 3 months of the evaluation period and could be adjusted for the following 3 months in case of inadequate seizure control or side effects. The comedication remained unchanged from baseline to the end of the 6 month evaluation period.

2.2. Pharmacokinetics data

Among the 46 children included in a population pharmacokinetics study previously published,[28] we selected the 21 for whom LVT plasma trough concentrations were available at 3 months. Blood samples were collected before the morning dose of LVT and the assay for LVT was performed using high pression liquid chromatography with UV detection.

2.3. Data analysis

Analysis was performed on an intention to treat basis. Patients with lost of follow-up, lack of efficacy, adverse events and deviation protocol were considered as non responders. Efficacy was assessed in the overall population at 3 and 6 month LVT based on seizure frequency normalized for 30 d (1) by comparing seizure frequency at baseline with the frequency during the second and third month evaluation period (primary endpoint) and during the last 3 month evaluation period, (2) by evaluating the number of responders during the same evaluation periods (i.e. more than 50% reduction of seizure frequency on LVT compared to baseline), and (3) by evaluating the number of seizure free children. The responder rate was also evaluated at 3 and 6 months according to epilepsy syndrome. Finally, among the responders at 6 months, mean percentages of seizure frequency decrease at 3 and 6 months (compared to baseline) were compared using a paired Student's *t*-test.

Univariate and multivariate analyses were conducted to identify factors associated with the LVT response at 3 months using logistic regression. The following factors were considered: age ($\leq$6 *vs* >6 years), sex, number of associated AEDs (1 *vs* 2 or 3) and seizure frequency at baseline, number of AED failures in the past 6 months, and duration, type (generalized *vs* partial) and etiology (symptomatic, cryptogenic or idiopathic) of epilepsy.

Safety was assessed in the overall population based on the adverse events reported by individuals and caretakers on standardized side effect questionnaires.

Efficacy/safety to LVT plasma concentration relationship was also assessed at 3 months.

All categorical variables were expressed as percentage and numbers, and continuous variables were expressed as median with first and third quartile (Q1–Q3). Unpaired median comparisons were realized with the Mann–Whitney *U* test. Statistical analysis was performed using Stata/SE 10.0 software (Stata Press, College Station, TX, USA).

3. Results

LVT was administered to 102 children within the study over a 3 year period. Patients' demographics are listed in Table 1. About half the patients were aged between 6 and 12 years while 18% were adolescents and 6% infants. Forty five percent had a brain lesion and had epilepsy for more than 2 years. Two-third of them had failed on at least one AED during the previous 6 months, mainly clobazam (22%), topiramate (18%), vigabatrin (12%) or lamotrigine (11%). Median seizure frequency was over one seizure a day. Most patients received two concomitant AEDs, the most commonly associated being valproate (52%), lamotrigine (33%), clobazam (28%), vigabatrin (17%) and topiramate (13%). Epilepsy syndromes are listed in Table 2: 41% of patients were diagnosed as partial epilepsy, 35% as Epilepsy with POS (81% were symptomatic, 19% were cryptogenic, none presented with idiopathic partial epilepsy) and 6% as CSWS (presenting with generalized and partial seizures), the following groups were generalized epilepsies, Infantile spasms (16%), childhood absence epilepsy and Dravet syndrome around 10%, 6% of Myoclono-astatic epilepsy (Doose syndrome), and 13% of other generalized epilepsy (mainly symptomatic generalized epilepsies not classifiable into a known syndrome).

The flow chart of the retention rate in the study is in Fig. 1.

3.1. Efficacy

The responder rate was 36% (37/102) and 32% (33/102) respectively at 3 and 6 month LVT, including 6 (5.8%) patients seizure free at 3 months and 7 (6.8%) at 6 months. Six patients (5.8%) were aggravated at 3 and 6 months with over 50% increase in

Table 1
Baseline demographics and clinical characteristics ($n = 102$).

Baseline characteristics	
Sex, *n* (%)	
Boys	58 (57)
Girls	44 (43)
Age, *n* (%)	
≥6 months, ≤2 years	6 (6)
>2 years, ≤6 years	31 (30)
>6 years, ≤12 years	47 (46)
>12 years, ≤15 years	18 (17)
Previous duration of epilepsy, in years, median (IQR)	5 (2–7)
Epilepsy etiology, *n* (%)	
Symptomatic	54 (53)
Cryptogenic	46 (45)
Idiopathic	2 (2)
Type of seizures, *n* (%)	
Partial	37 (36)
Generalized	64 (63)
Undefined	1 (1)
Number of AED failure and stopped during the previous 6 months before the inclusion, *n* (%)	
0	42 (41)
1	34 (33)
≥2	26 (26)
Number of seizure per month at baseline, median (IQR)	53 (12–167)
Number of associated AED at baseline, *n* (%)	
One	21 (20)
Two	75 (74)
Three	6 (6)

seizure frequency compared to baseline. Among the 33 responders at 6 months, seizure frequency decreased in mean by 66% (95%CI [55–76]) at 3 month LVT and by 79% (95%CI [69–87]) at 6 months compared to baseline (p paired Student's t-test <0.01).

The median dose of LVT was 30.0 mg/kg/d at 3 months ($n = 79$, Q1–Q3: 21.5–43.5 mg/kg/d) and 31.1 mg/kg/d at 6 months ($n = 59$, Q1–Q3: 25.0–44.8 mg/kg/d), with 3 responders at doses under 10 mg/kg/d at 3 months and 2 at 6 months. Among children receiving more than 40 mg/kg/d ($n = 29$), 66% were non responders and 17% presented with seizure aggravation.

Table 2
Epilepsy syndromes ($n = 102$).

Epilepsy syndrome	*n* (%)	Median age (years)	Age range (years)
Epilepsy with partial onset seizures	36 (35)	7	1–16
West syndrome	16 (16)	6	0.75–13
Childhood absence	12 (12)	9	3–15
Dravet syndrome	9 (9)	8	3–14
Myoclonic astatic epilepsy	6 (6)	5	4–9
Continuous spikes and waves during sleep	6 (6)	10	6–13
Lennox–Gastaut syndrome	3 (3)	12.5	12–15
Other generalized epilepsy	14 (13)	6	1–16

At 3 month LVT, patients with CSWS exhibited the highest responder rate (67%, 4/6) with 3 patients being seizure free and no patient aggravated (Fig. 2). For absence epilepsy, the responder rate was 42% (5/12), and for Epilepsy with POS it was 39% (14/36), respectively 14% and 45% in cryptogenics and symptomatics (difference not significant), with 2 seizure free patients. Responder rate was 33% (2/6) for myoclonic-astatic epilepsy, including 1 seizure free, and 36% (5/14) for the other generalized epilepsies. Within the small sample of patients with Lennox–Gastaut patients syndrome, 1/3 responded. One to 2 patients were aggravated in all of these syndromes except for Myoclono-astatic epilepsy, Dravet syndrome and Lennox–Gastaut syndrome. The lowest responder rate was for Infantile spasms (31%, 5/16) and Dravet syndrome (11%, 1/9), for which no patient became seizure free whereas 2 with Infantile spasms were aggravated.

At 6 month LVT (Fig. 2), patients with CSWS still exhibited the highest unchanged responder rate: the 4 responders (3 seizure free and 1 with 92% seizure reduction) showed behavioral and cognitive improvement, 2 had normal EEG and 2 remained with CSWS. For absence epilepsy and Epilepsy with POS the responder rate decreased compared to 3 month rate reaching respectively 33% (4/12) and 25% (9/36), keeping 1 seizure free patient and 36%

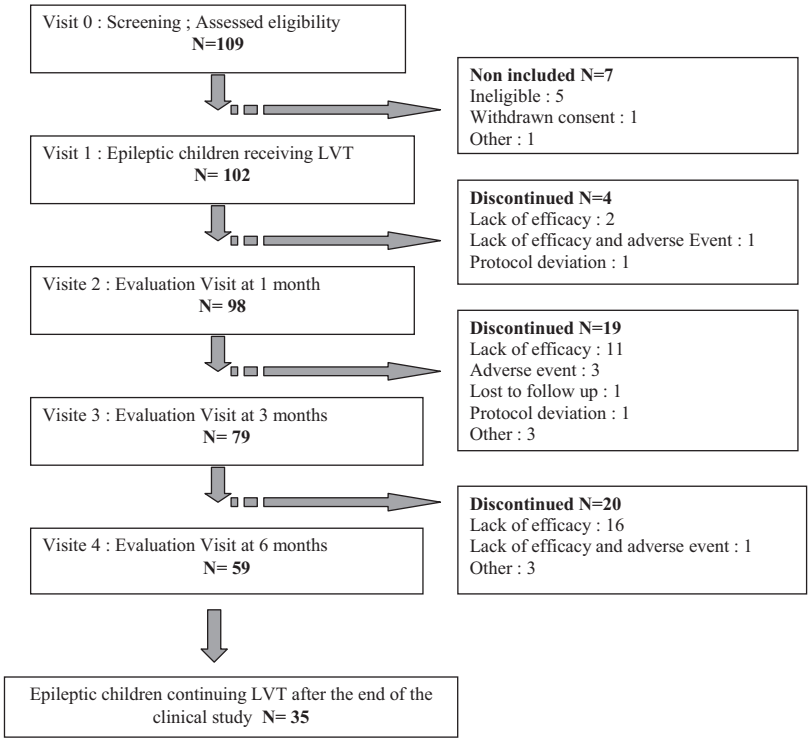

Fig. 1. Flow chart of the trial.

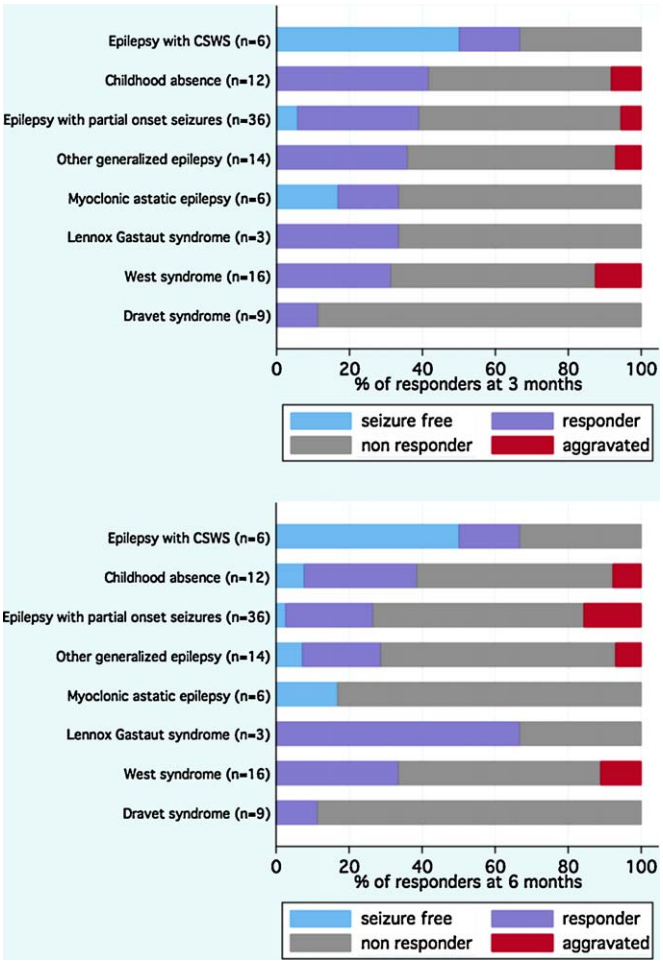

Fig. 2. Response at 3 and 6 months on levetiracetam according to epilepsy syndromes.

responders in symptomatics but none in cryptogenics (difference not significant). One patient escaped for myoclonic-astatic epilepsy (the other one remained seizure free) and for the other generalized epilepsies, whereas there was one more responder for Infantile spasms). Efficacy was maintained in the unique responders presenting with Dravet syndrome and Lennox–Gastaut syndrome.

The univariate and multivariate analyses did not show different responder rates in seizures classified as partial (41%, 15/37, OR = 1.3) or generalized (34%, 22/64, OR = 1) (Table 3). Neither the previous duration of epilepsy nor the number of comedications, two markers of the severity of epilepsy, were associated with the response to LVT. Only the age tended to be a significant predictor of response with better efficacy for children aged over 6 years (OR = 2.40, $p = 0.06$).

3.2. Safety

Thirty-three adverse events were attributed to LVT at 3 months and 39 at 6 months, 19 patients presenting with 2 or 3 adverse events (Table 4). For 5.9% (6/102 patients) the events were reported as severe and 4.9% (5/102) patients stopped LVT prematurely for intolerability. The most frequently reported side effects were hyperexcitability (17.5%), sleep disorders (12.6%) and drowsiness (11.7%). Their frequency tended to be higher at 6 than 3 months on LVT, due to the attempt to increase the dose over 40 mg/kg/d after 3 months in the non-responders. However, we did not find any significant correlation between dose and behavior tolerability.

3.3. Efficacy/tolerability – plasma level relationship

The LVT plasma trough concentrations obtained at 3 months involved 11 children with Epilepsy with POS, 4 with CSWS, 3 with Infantile spasms, 1 absence, 1 Dravet syndrome and 1 other generalized epilepsy. The median age of these 21 patients was 11.5 years (4.5–15.9 years). The median trough concentration was 7.2 mg/L (Q1–Q3 4.7–10.2 mg/L). Non responders ($n = 8$) showed

Table 3
(a) Factors associated with LVT response at 3 months and (b) LVT response at 3 and 6 months in "Epilepsy with partial onset seizures" subgroup according to etiology.

		Univariate analysis			Multivariate analysis ($n = 102$)		
	n	OR	95% CI	*p*	OR	95% CI	*p*
(*a*)							
Sex							
Boys	22/58	1			1		
Girls	15/44	0.85	0.37–1.92	0.69	0.85	0.36–1.97	0.71
Age							
≤6 years	9/37	1			1		
>6 years	28/65	2.35	0.96–5.77	0.06	2.38	0.96–5.88	0.06
Type of epilepsy							
Generalized	22/64	1			1		
Partial	15/37	1.30	0.56–2.99	0.54	1.25	0.52–3.00	0.62
Etiology of epilepsy							
Cryptogenic	15/46						
Symptomatic	21/54	1.31	0.58–2.99	0.51	–		
Duration of epilepsy							
<6 years	19/58	1			–		
≥6 years	18/44	1.46	0.65–3.28	0.36	–		
Number of associated AED							
1	7/21	1			1		
2 or 3	30/81	1.17	0.43–3.24	0.75	1.26	0.43–3.64	0.67

	At 3 months				At 6 months			
	n (%)	OR	95% CI	*p*	*n* (%)	OR	95% CI	*p*
(*b*)								
Cryptogenic	1/7 (14.3)	1			0/7 (0)	1		
Symptomatic	13/29 (44.8)	4.9	0.52–45.8	0.21	10/29 (35.5)	8.1	0.42–155	0.15

Table 4
Adverse events occurred during the clinical study ($n = 102$).

	All adverse events at 3 months	Adverse events related to LVT at 3 months	All adverse events at 6 months	Adverse events related to LVT at 6 months
At least one adverse event (AE)				
Yes	44	33	48	39
Number of different types of AE				
1	26	20	23	20
2	9	9	13	14
≥3	9	4	12	5
Type of AE				
Loss of appetite	9	7	10	8
Weight loss	5	1	5	1
Abdominal pain	4	0	5	1
Nausea	1	0	2	1
Vomiting	5	3	6	3
Diarrhea	5	3	7	3
Drowsiness	11	10	14	12
Hyperexcitability	20	15	22	18
Sleep disorders	10	9	14	13
Hypotonia	1	1	2	1
Ataxia	5	5	5	5
Tremor	3	1	5	2

significantly higher median plasma concentrations than responders ($n = 13$), respectively 10.1 mg/L (Q1–Q3 6.9–16.1 mg/L) and 5.4 mg/L (Q1–Q3 4.68–10.2 mg/L) (Mann–Whitney U test, $p = 0.03$). Two non responder patients had the two highest concentrations (>17 mg/L). No difference was evidenced in plasma concentrations between responders and non responders in Epilepsy with POS ($n = 11$) and in CSWS ($n = 4$), but sample sizes were small. Regarding safety, no significant association was found between adverse effects and plasma trough concentrations.

4. Discussion

Although LVT is currently extensively prescribed in childhood epilepsy, the panel of refractory epilepsy syndromes has not been entirely evaluated prospectively. In the present exploratory trial according to syndromes, epileptic encephalopathy with CSWS discloses the highest benefit of LVT as adjunctive therapy. We also confirm the good response in Epilepsy with POS and suggest that neither Doose nor Lennox–Gastaut patients are at risk of aggravation, two conditions that share clinical features of CSWS (drop attacks, cognitive deterioration and generalized spike waves) and with which the diagnosis at onset may occasionally be difficult in childhood. The age over 6 years tends to be a predictive factor of response sustaining a poor response in Infantile spasms and Dravet syndrome. Tolerability is excellent up to a maximal dose of 40 mg/kg/d. In spite of a limited sample, we assume that our results in CSWS, together with those gathered from several convergent retrospective reports, provide a valuable rational to design a randomized-controlled trial with LVT dedicated to this syndrome.

The strategy of pediatric development for LVT has clearly followed the classical pathways. However, a first prospective trial of this kind was recommended by the Commission of drugs of the International League Against Epilepsy many years ago (ILAE Commission, 1994), and has now become mandatory according to the EMEA guidelines (www.ema.europa.eu, Aug 2010). Had this been followed, the compound would have gathered arguments to become the first line drug as an alternative to valproic acid for children[13]: it is well tolerated, has large range of efficacy and does not aggravate significantly specific epilepsy syndromes. In addition, it comprises neither the disadvantage of altering the metabolism of comedication or being altered by comedication, nor the risk of revealing an inborn error of metabolism, conditions that, although they are rare, are often revealed by epileptic seizures and challenging for both diagnosis antiepileptic drug treatment strategy.

Among the open-labeled series of children treated with LVT for pharmaco-resistant epilepsy only two are prospective and consider epilepsy syndromes.[9,15] Efficacy data in our overall population are comparable to those of both: respectively 36% and 32% *vs* 39% and 49% of responders, 6% and 7% *vs* 9% and 4.5% of seizure free rate, and 7% *vs* 11% and 15% of patients aggravated. Tolerability was quite good in our population, with hyperexcitability and drowsiness as most frequent adverse events from infancy to late childhood, as reported at any age, including the placebo-controlled trials.[1,2,7,9,15,17,18] Our median LVT dose also is similar to that of the two other prospective trials, 34 *vs* 33 and 36 mg/kg/d. As far as children over 4 years are concerned, this dose gave plasma concentrations in the same range as previously reported in adults and children.[20,29] However higher LVT doses did not improve the patients in our series and even induced a seizure worsening in some of them, so that we would advice 40 mg/kg/d as the maximum dose rather the 60 mg/kg/d targeted from age 4 in partial onset seizures as previously recommended.[30]

We found a similar efficacy rate in partial and generalized epilepsy syndromes, which is consistent with the large spectrum of action extensively described with LVT and predictable from its mechanism on the synaptic vesicle protein SV2A.[31] However, different epilepsy syndromes do not get the same benefit from LVT: CSWS and absence epilepsy get the highest, Infantile spasms and Dravet the lowest. The efficacy rate we observe in refractory absences is comparable to that of a prospective Italian series.[32] Age over 6 years is a significant factor for efficacy in our study, and LVT is indeed disappointing in Infantile spasms and Dravet syndrome. Altogether, among the 23 patients with Infantile spasms prospectively reported with LVT as adjunctive therapy (adding Lagae and Grosso's patients to our series), none became seizure free, a requirement for this severe epileptic encephalopathy. Even in newly diagnosed cases, few patients were controlled (2/5) on LVT.[33] LVT seems therefore definitely poor in Infantile spasms. On the other hand, the encouraging results obtained in a prospective Italian series of 28 Dravet patients[16] contrast with the poor efficacy in our series. However, we presume that our Dravet patients were more pharmacoresistant cases since they all had previously received stiripentol compared to only 7% for the Striano series.

By contrast, LVT shows an efficacy signal in CSWS with 2/3 responders and 50% becoming seizure free at 3 months of treatment. Although our sample is small, these prospective results are consistent with the favorable findings of several retrospective reports: Capovilla et al. reported 3 patients in 2004,[23] and soon after there were 4 other series of respectively 12, 6, 17 and 4 CSWS children, including symptomatic cases and idiopathic CSWS in the context of BECTS without seizures.[24–27] Overall, seizure frequency decreased by over 50% in 21/35 (60%) patients whether CSWS was symptomatic or idiopathic. EEG discharges also decreased by 75% to 100% in a majority of patients, while behavior and cognition improved.[24,26] Our trial was not initially designed to focus on CSWS so that prospective evaluations of sleep EEG and behavior/cognition were not planned, although they should replace seizures as primary endpoints in a syndrome-dedicated study. As in Infantile spasms, seizures may be considered a target symptom in CSWS: although their control is not sufficient to cure the child, their persistence certifies that EEG is still abnormal and that the cognitive risk persists.

Few AEDs may control CSWS, but none of them proved to be efficient in a randomized procedure, namely benzodiazepines, ethosuximide, sulthiam[34] and mainly high doses of steroids[35] for which there are life-threatening safety concerns. In addition, some

of these drugs are poorly efficient on the focal seizures that are frequently associated with symptomatic CSWS. Alternatively the AEDs of choice in focal seizures may aggravate CSWS, particularly carbamazepine and oxcarbazepine, with occurrence of negative myoclonus.[36] In the context of BECTS, there is a risk of seizure and EEG aggravation when using phenobarbital or carbamazepine, and also lamotrigine to some extent.[37,38] LVT has the advantage to be efficient on focal seizures, in both symptomatic and idiopathic forms,[15] and to prevent any worsening in CSWS and BECTS.

Finally, we did not find any case of aggravation using LVT in Myoclono-astatic epilepsy or in Lennox–Gastaut syndrome, two syndromes which also present with drop attacks and whose features are quite close to CSWS features, at least at onset (ILAE classification). With 33% responder patients in the former, our findings are less favorable than suggested in one retrospective series of 23 patients with Myoclono-astatic epilepsy.[39] However, our sample is small, and one patient became seizure free.

Based on these arguments and considering that half the 48 CSWS patients refractory to other drugs and entered into our prospective and the retrospective studies improved, we assume that LVT is definitely a good candidate for CSWS. However, despite the need for new therapeutic agents, no randomized-controlled trial has involved CSWS syndrome so far. The condition of *orphan therapeutics* of this severe epilepsy is a big concern if we consider that controlling epilepsy can minimize the cognitive sequelae. The suggested efficacy of LVT we presently highlight using a prospective exploratory approach should be the main step before a confirmatory trial.

Conflict of interest

No author has any conflict of interest for this study.

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